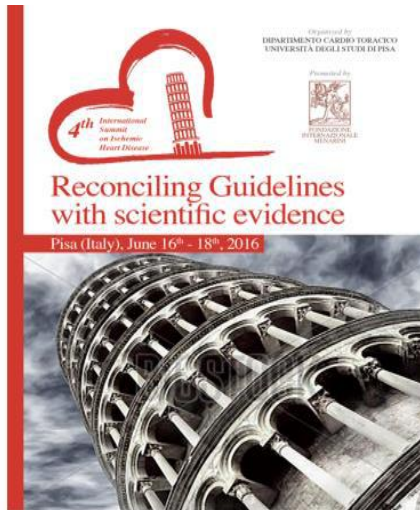


**4th International
Summit on
Ischaemic Heart Disease
Reconciling Guidelines with scientific evidence
Pisa (Italy), June 16-18, 2016
Highlights**

Introduction



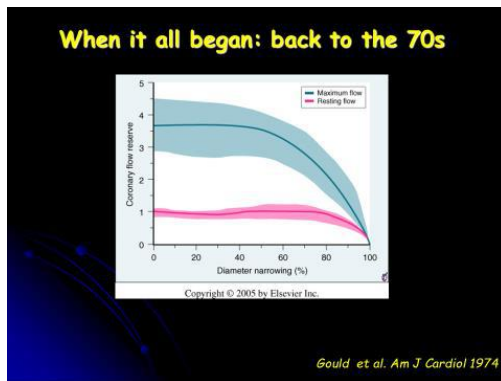
Prof. Marzilli, chairman of the convention, opened the summit by stressing the international validity of this initiative in which various world opinion leaders in this sector were participating. The speaker expressed his hope that everyone attending would be able to contribute in an effective and concrete manner towards achieving the objective of the convention, and namely, that of launching a new theory, aptly called Copernican, regarding the meaning, essence, diagnosis and treatment of ischaemic heart disease.

To follow the presentations of this convention just click on this link:

<http://www.fondazione-menarini.it/Archivio-Eventi/2016/4th-International-Summit-on-Ischemic-Heart-Disease-Reconciling-Guidelines-with-scientific-evidence/Materiale-Multimediale>

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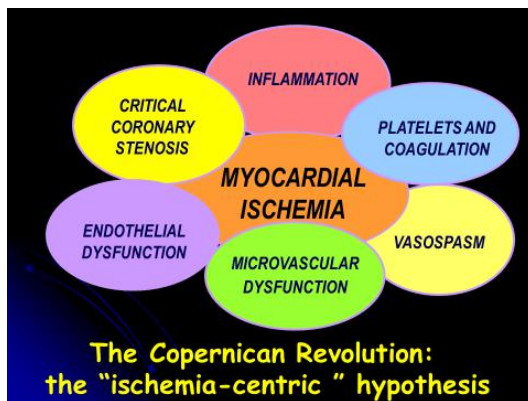
What we still don't know about ischaemic heart disease



During his opening talk, Prof. Marzilli from Pisa (I) analysed the link between ischaemic heart disease and coronary disease, a link that is not as close as we originally believed in the past. The speaker pointed out how the condition of angina is not always unequivocally supported by the presence of atherosclerotic lesions at the level of the coronary tree, just as coronary sclerosis is not always accompanied by angina-type signs and symptoms. Ischaemic heart disease is the focal point of a whole series of physiopathological phenomena of which coronary sclerosis is merely one of the components.

Low diagnostic yield of elective coronary angiography
Patel et al, NEJM 2010, 362:886-95

1. No consistent association between stenosis and ischemia
2. No consistent association between stenosis and angina
3. A linear association between coronary atherosclerosis and Framingham risk score



Other factors include any inflammatory conditions, endothelial dysfunction, coagulopathies, microvascular dysfunction and vasospasm. These data render the main guidelines regarding the issue of ischaemic heart disease obsolete as they continue to base their assessments solely on the correlation between ischaemic heart disease and coronary disease.

- Why are ischaemic heart disease and coronary disease both pathologically distinct?
- What are the main mechanisms of myocardial ischaemia?
- What are the main characteristics of the "ischaemic-centric" theory?
- What is the real prevalence of cardiovascular disease compared to that of the theory hypothesised by the guidelines?
- What are the characteristics of the tests normally conducted in the diagnosis of cardiovascular disease?
- Could the coronary anatomy be a predictive factor of the condition of myocardial perfusion?

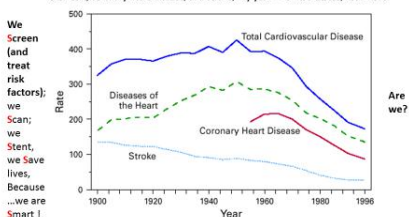
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New trends in the treatment of ischaemic heart disease: illusion or reality?

FIGURE 1 Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996



*Per 100,000 population, standardized to the 1960 U.S. population.
†Diseases are classified according to International Classification of Diseases (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1950, 1980, 1986, 1989, 1996, and 1999. Death rates before 1929 do not include all states. Comparability ratios were applied to rates for 1970 and 1975.
Source: Adapted from reference 1; data provided by the National Heart, Lung and Blood Institute, National Institutes of Health.

While on one hand the prevalence of disease has significantly reduced over the years, on the other however, it is evident that this success is not always due to an improvement in the diagnostic/therapeutic strategies, but instead to other factors

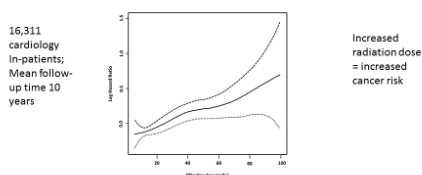


Fig 2 Log hazard ratio for cancer onset plotted against effective dose below 100 mSv, adjusted for age, sex, and smoking habit. The line was estimated using a smoothed function (generalized spline) of effective dose in the Co-metast.

Clara Cappagliani, Giuseppe Rossi, Patrizia Landi, Claudio Michelassi, Marco Barnabita, Laura Congiani, Eugenio Picano
Long-term outcome and medical radiation exposure in patients hospitalized for cardiovascular disease
International Journal of Cardiology, Volume 195, 2015, 30–36
<http://dx.doi.org/10.1016/j.ijcard.2015.05.080>

Prof. Picano from Pisa (I) presented extremely interesting data on the epidemiology of ischaemic heart disease, the use of the main instrumental diagnostic tests and the use of cardiac imaging as the principal prevention instrument. Contrasting elements emerge from their analysis: while on one hand the prevalence of disease has significantly reduced over the years, on the other however, it is evident that this success is not always due to an improvement in the diagnostic/therapeutic strategies, but instead to other factors linked for example to lifestyle and more particularly, to the quality of the air we breathe. The speaker highlighted the presence of significant correlations between the diagnostic/therapeutic interventions and the risk of both cardiovascular disease and ischaemic cardiomyopathy and the death rate due to both these causes.

Air quality control measures in Spain and projected mortality reduction (2007–2014)

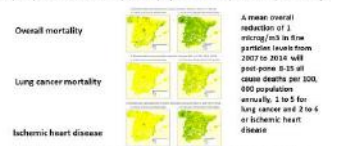


Fig 2. Assessment of the overall mortality reduction of a reduction in the particulate matter (PM10) in Spain. No mortality reduction was seen (year 2007) provided (year 2014). PM10 in air quality, also called PM2.5.

Clara Ricci et al.

An overall mortality and mortality impact of fine particulate matter pollution in Spain
Environmental Research, Volume 150, 2014, 15–20
<http://dx.doi.org/10.1016/j.envres.2015.11.008>

A good mayor can be more important than a good cardiologist for protecting your heart, since urban viability is more relevant than myocardial viability

- By how much is the prevalence of ischaemic heart disease reduced in the general public for every microg/m³ less of fine particles in the air breathed in?
- What is the effect of radiotherapy on the prevalence of cardiovascular disease?
- Why has there been an increase over the years in the use of the echo stress technique compared to the imaging techniques based on the perfusion of the myocardium?
- What correlation exists between the neoplastic risk and the radioactive dose absorbed in patients subjected to diagnostic techniques based on myocardial perfusion?
- How has the position of the Ministry of Health changed with regard to the unconditional application of the preventive strategies based on cardiac imaging?

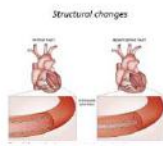
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Microvascular dysfunction: a new therapeutic target?

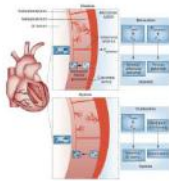
Mechanisms of Coronary Microvascular Dysfunction "Vascular"



Camici PG, DiCorleto PE, Rossi G. *J Am Coll Cardiol*. 2015;55(1):108-17.

tunica intima and tunica media of the blood vessels; vascular with functional non-structural alterations of the vascular parts; extravascular, where the alterations are found in the

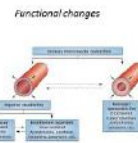
Mechanisms of Coronary Microvascular Dysfunction "Extra-vascular"



Camici PG, DiCorleto PE, Rossi G. *J Am Coll Cardiol*. 2015;55(1):108-17.

Prof. Camici from Milan (1) addressed the issue of the microvascular dysfunction, viewed as a new therapeutic target, starting from the consideration that there are three types of physiopathogenetic mechanisms underlying this disease: vascular with structural alterations of the microcirculation, that is, in the intramural arterioles. The speaker presented data on the main symptomatological and physiopathological situations linked to these three conditions.

Mechanisms of Coronary Microvascular Dysfunction "Vascular"



Camici PG, DiCorleto PE, Rossi G. *J Am Coll Cardiol*. 2015;55(1):108-17.

- What are the main physiopathological conditions responsible for the onset of the microvascular dysfunction?
- What is the main symptom of microvascular dysfunction of the vascular type?
- How important is the phenomenon of remodelling the coronary arterioles in determining microvascular dysfunction?
- What is the effect of the ACEi treatment on the myocardial flow?
- What are the mechanisms underlying the non-structural microvascular dysfunction?
- What are the extra-vascular mechanisms that give rise to the microvascular dysfunction?

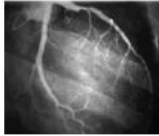
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Microvascular dysfunction: the prevalence and the diagnostic indicators of disease.

Currently the management of IHD is based on the paradigm that myocardial ischaemia is caused exclusively by atheromatous CAD

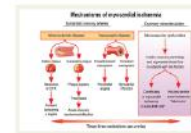


CAD in the absence of myocardial ischaemia = false negative
Ischaemia in the absence of CAD = false positive

Prof. Kaski from London (UK) addressed the topic of microvascular dysfunction, starting from epidemiological data and touching the main aspects linked to its physiopathology, symptomatology, diagnosis and treatment. In this way he was able not only to confute the theory still

MVD and Refractory Angina

Coronary microvascular dysfunction -in the presence or absence of obstructive epicardial coronary artery disease- may be an important cause of "refractory" angina



Coronary microvascular dysfunction can be associated with all conventional CAD risk factors and with obstructive CAD itself.

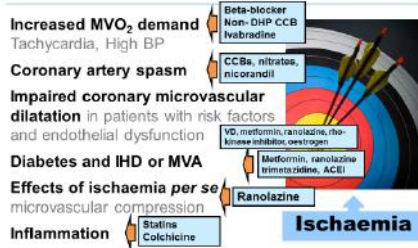
Coronary 7 (16). Eur Heart J 2010

based on the centrality of the atheromatous plaque, but also to analyse the correlation between microvascular dysfunction and spasm and the presence of refractory angina. In the second part of his talk, Prof. Kaski gave a description of the causes and the current therapeutic options

for the treatment of refractory angina, specifying that despite being limited, it is necessary to do everything possible for gaining control of the angina symptomatology.

Stable Angina: Treatment Targets

(Scenario: Stable angina - no indication for PCI/CABG or patient not suitable for intervention)



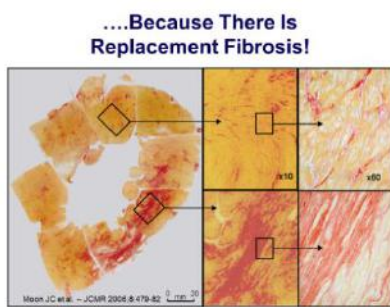
- What is the main definition of refractory angina?
- What is the prevalence of re-vascularised patients who still show symptoms of angina?
- What is the correlation between microvascular dysfunction and refractory angina?
- What does microvascular angina mean?
- What is the pathogenesis of coronary microvascular dysfunction?
- What are the main therapeutic targets of refractory angina?
- What are the therapeutic protocols used in the treatment of refractory angina?

To find the answer to these and other questions just click on this link:

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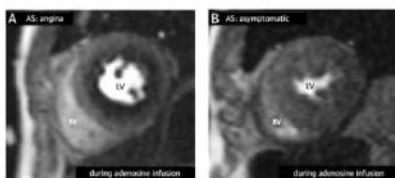
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Microvascular coronaropathy within the context of ischaemic heart disease

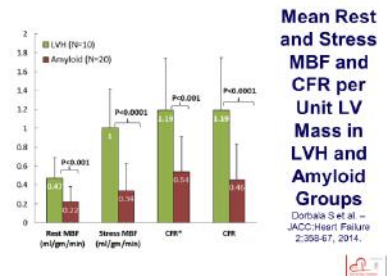


CMD as a Mechanism of Angina in Severe AS

Ahn J-H et al. - J Am Coll Cardiol 2016; 67:1412-22.



Prof. Sechtem from Stuttgart (D) spoke about microvascular coronaropathy and its interactions with other heart diseases, some of which are rare. In particular, the speaker addressed the correlation between microvascular dysfunction and Fabry disease, amyloidosis, dilatative cardiomyopathy and aortic stenosis. He addressed the different morphological situations that are secondary to the presence of microvascular dysfunction and the therapeutic implications linked in particular to the simultaneous presence of microvascular dysfunction and aortic stenosis, even when not severe.



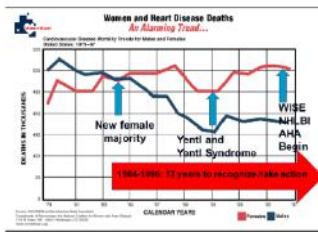
- What was the pathophysiologic hypothesis presented by the speaker for explaining the link between the accumulation of glycolipids in the coronary arteries and the presence of myocardial fibrosis in patients suffering from Fabry disease?
- What are the signs of the presence of microvascular dysfunction in patients suffering from amyloidosis?
- What is the pathophysiologic mechanism linking the microvascular dysfunction with the dilatative cardiomyopathy?
- Can microvascular dysfunction trigger episodes of angina in patients suffering from severe aortic stenosis?
- What are the pathophysiologic mechanisms that give rise to the presence of microvascular dysfunction in patients suffering from aortic stenosis?

To find the answer to these and other questions just click on this link:

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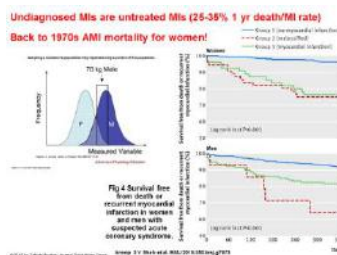
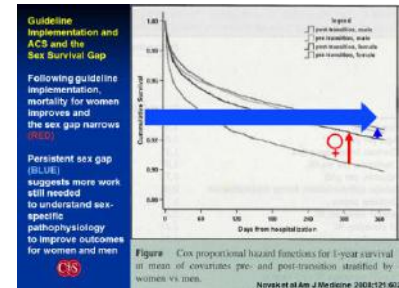
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Ischaemic heart disease conjugated in the female tense: Monet versus Manet



Prof. Bairey-Merz from Los Angeles (USA) addressed this subject starting from a comparison between two artists who, despite using similar pictorial techniques and both preferring female figures as the subjects of their paintings, produced artworks that are radically different, namely, Monet and Manet. In the same way, ischaemic heart disease, despite

representing a nosological entity that is well defined, actually occurs in a significantly different manner in men compared to women and exposes the female gender to far more severe complications and outcomes. The speaker addressed this issue starting from mortality and morbidity data, which are profoundly different from one gender to the other.



she then went on to point out the scarcity of female patients enrolled in all types of clinical cardiovascular studies, also emphasising the need to implement guidelines capable of recognising the female situations of cardiovascular disease, in order to improve the outcome of disease.

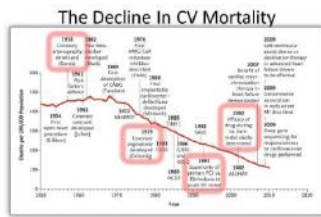
- Why, according to the speaker, is there a gap in terms of cardiovascular mortality and morbidity between men and women?
- At what age does the prognosis for cardiovascular disease get worse in women?
- What differences exist between men and women in terms of the treatment of the disease and the prevalence of fatal events?
- What is the prevalence of coronaropathic patients of the female gender enrolled in controlled randomised studies?

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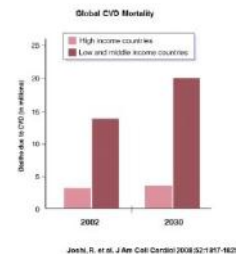
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The use of the diagnostic coronary angiography in ischaemic heart disease

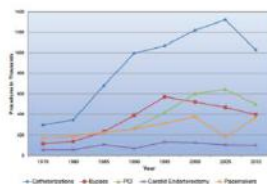


Robins EG and Braunholtz H. *Lancet* 1992; 339:654-61

Prof. Weintraub from Newark (USA) addressed this topic starting from the consideration that over the years there has been a significant reduction in the incidence of myocardial infarction, in particular in the form characterised by ST elevation. This result has been obtained thanks to the implementation of various combined strategies, the most important of which has been the reduction of the risk factor via the modification of the patient's lifestyle and a reduction in the levels of environmental pollution. In other words, the invasive diagnostic tests, including the coronarography, have contributed in a decidedly lesser extent towards reducing the incidence of myocardial infarction. The coronary angiographic technique, developed during the latter half of the nineties, continues to be commonly used as the main diagnostic solution in patients suffering from every degree of ischaemic heart disease. When appropriate, its application still remains valid. Nevertheless, other valid options exist consisting of new diagnostic methods that are non-invasive and the application of which is supported by guidelines and by the same principles underlying clinical epidemiology. The speaker stressed the importance of acquiring greater confidence in these alternative methods in order to reduce the inappropriate use of catheterisation for diagnostic purposes and thereby improve the outcome of these patients.



Joshi N, et al. *J Am Coll Cardiol* 2008;52:1817-1825



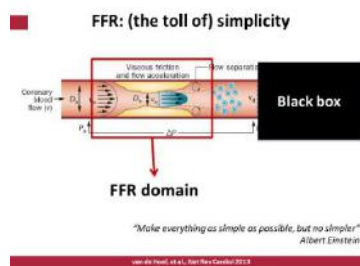
- What are the main achievements that contributed in a determining manner to the reduction of the cardiovascular death rate?
- What is the expected global prevalence of the cardiovascular death rate in low-income countries for the year 2030?
- What are the recommendations of the guidelines regarding coronary angiography?
- What are the main limitations of the coronary angiography?
- How reliable is the coronary angiography?

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Coronary flow vs. coronary pressure: what are the optimal parameters for ensuring a correct assessment of the clinical picture?

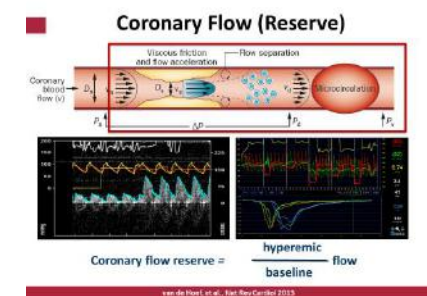
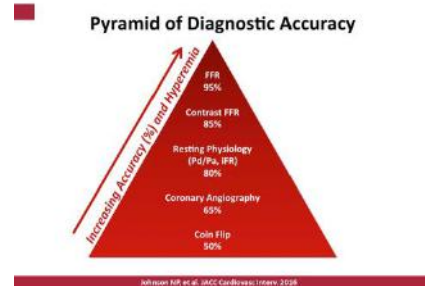


Prof. Van De Hoef from Amsterdam (NL) addressed this extremely topical issue and presented interesting data on the reproducibility and accuracy of the flow fractioning reserve test (FFR), by comparing it with the coronary flow reserve test (CFR) and evaluating the pros and cons of the two tests. The

speaker dedicated his talk to the presentation of clinical and haemodynamic data for the

purpose of providing a

correct assessment of the applicability of both tests in the clinical field. In his conclusion, Prof. Van De Hoef emphasised how in haemodynamic terms, ischaemic heart disease is a complex disease that cannot be explained merely on the basis of the role carried out by the epicardium in regulating the coronary circulation.



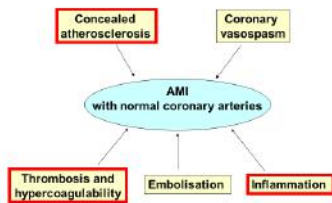
- What are the main characteristics of the coronary flow reserve test?
- Why, according to the speaker, should the test based on the study of the coronary flow be the first line test for the diagnosis of ischaemic heart disease?
- What role can be played by the tests based on the study of the coronary pressure in the diagnosis of ischaemic heart disease?
- What are the limits of the test described by the speaker based on the measurement of the coronary pressure?

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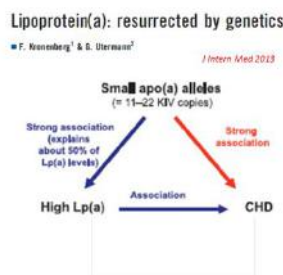
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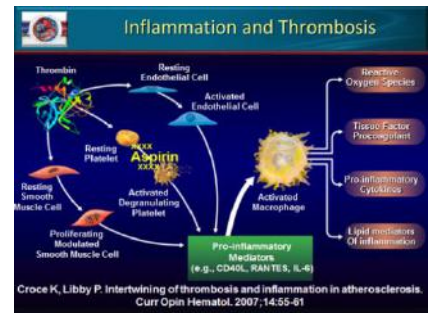
The pathogenesis of the myocardial infarction: multiple mechanisms face to face



He described the phenomena of thrombosis, hypercoagulability and inflammation, underscoring the intimate link between thrombosis and inflammation. Under a



Prof. De Caterina from Chieti (I) addressed the topic of the pathogenesis of myocardial infarction, taking time to describe the main mechanisms responsible for the onset of the disease. The speaker presented data on the potential mechanisms that trigger the onset of infarction in the presence of lesion-free coronaries.



physiopathogenetic profile, the in-depth analysis of the correlation between these mechanisms, together with the presentation of data gleaned from studies conducted by his research group, made it possible for the speaker to point out in his conclusions how patients with angina and normal coronary arteries have a higher risk of developing myocardial infarction and fatal events than angina patients with atherosclerotic lesions of the coronary tree.

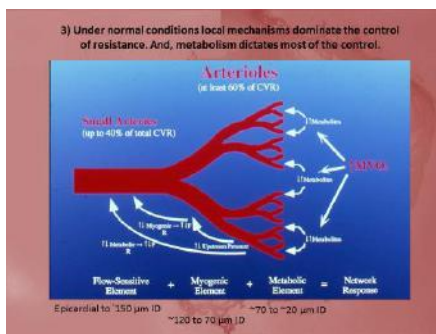
- What correlation exists between inflammation and coronary thrombosis?
- What is the role of Lp(a) in determining athero-thrombotic phenomena?
- Is there a particular genetic pattern that acts as a risk factor for athero-thrombotic coronary?
- What are the factors that influence the prognosis of patients suffering from angina?

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New critical factors in regulating the coronary microcirculation

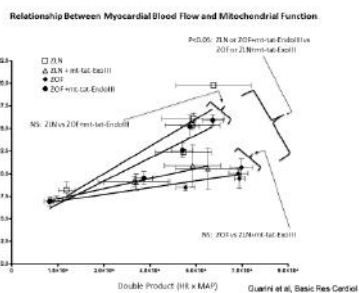


channels in particular stand out, as they are sensitive to the are responsible for induced metabolic coronary dilatation.

Prof. Chilian from Rootstown (USA) addressed this topic starting from the viewpoint that the coronary microcirculation is characterised by a high and intrinsic complexity due to the fact that it is subject to coronary vascular resistance, which in turn is controlled by precise metabolic signals. He took time to describe the principals, amongst which the Kv1.5 out, as they are sensitive to the are responsible for induced metabolic coronary dilatation. speaker then described the



The mitochondrial function, defining it as fundamental for the metabolic control of the coronary flow. In the last part of his talk, Prof. Chilian demonstrated how the alteration of the link between metabolism and coronary flow is one of the causes contributing to the onset of heart failure.



- What are the main metabolic signals that control the coronary flow?
- What is the effect of 4-aminopyridine on the relationship between myocardial oxygen consumption and coronary flow?
- Why is the mitochondrial function essential for the metabolic control of the coronary flow?
- Why does the alteration of the link between metabolism and coronary flow trigger the onset of heart failure?

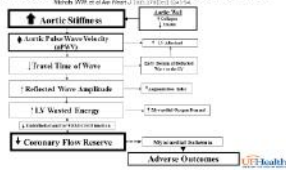
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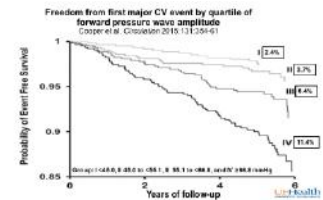
Non-atherosclerotic ischaemic heart: when to suspect it and how to diagnose it

Association of aortic stiffness and wave reflections with GFR in women without obstructive CAD: Ancillary study from WISE



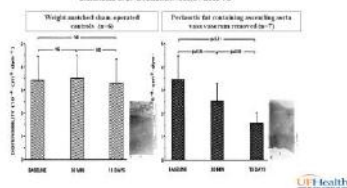
Prof. Pepine from Gainesville (USA) spoke about the diagnosis of non-atherosclerotic ischaemic heart disease starting from the knowledge acquired on this pathological form. The speaker addressed the correlation between left-ventricular hypertrophy, factors that predispose for the onset of atherosclerosis, and the coronary flow

reserve. He has arrived at the conclusion that the critical factor in non-atherosclerotic ischaemic heart disease is the vascular stiffness responsible for the dysfunction of the coronary microcirculation. The speaker concluded his talk by stating that it is necessary to increase our knowledge of the factors responsible for the increase in vascular stiffness and the



ageing mechanisms linked to cell sensitivity and the regulation of the extracellular matrix of the aortic wall in order to be able to implement early diagnosis of non-atherosclerotic ischaemic heart disease.

Aortic distensibility after vasa vasorum removal



- What is the correlation between atherosclerosis and the vascular flow reserve?
- What is the correlation that links arterial vessel stiffness with the coronary flow reserve?
- What is the effect of the removal of the vasa vasorum on aortic distensibility?
- How much does the anterograde pressure wave influence the likelihood of developing a major cardiovascular event?
- What are the main components of the haemodynamic load that have a correlation with the cardiovascular events?

To find the answer to these and other questions just click on this link:

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Coronary disease and the application of the “genetic risk score” in primary prevention

Human DNA Variation

Each human genome has 3 million SNPs which accounts for 80% of human variation, including predisposition to disease

Prof. Roberts from Phoenix (USA) addressed this extremely current topic starting from the fact that specific genetic mutations exist in more than 50% of subjects susceptible to developing coronary disease and 10% of cases of coronary disease that manifest earlier than the age of 50 are supported by genetic-type risk factors. The speaker then went on to

International Consortium for Genome Wide Association Studies of CAD

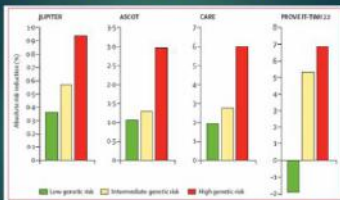
CARDIoGRAM

Coronary ARtery Disease Genome-wide Replication And Meta Analysis

talk about the origins of the mutations of the human DNA and in particular, the genetic variations responsible for coronary disease. In the second part of his talk, the speaker presented the data produced by the CARDIoGRAM study conducted by the International Consortium for Genome

Wide Association Studies of CAD, in which as many as 58 genetic variants for the risk of coronary disease were identified, after an analysis of the genomes in more than 200,000 patients. The speaker concluded his talk by stressing how the use of a genetic risk indicator for detecting the risk of coronary disease represents a radical improvement in the primary prevention of coronary disease.

GENETIC RISK VARIANTS PREDICT RESPONSE TO STATIN THERAPY IN EACH RISK GROUP



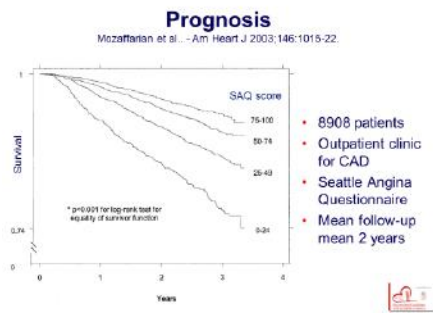
- How many are the new mutations per individual in every generation?
- How many mutations are present in our generation?
- What was the first genetic risk factor for coronary disease identified in 2007?
- What are the main implications for the prevention and treatment of coronary disease linked to the application of our knowledge in the genetic field?
- In the light of the genetic studies, what is the role of HDL in the determinism of coronary disease?

To find the answer to these and other questions just click on this link:

<http://www.fondazione-menarini.it/Archivio-Eventi/2016/4th-International-Summit-on-Ischemic-Heart-Disease-Reconciling-Guidelines-with-scientific-evidence/Materiale-Multimediale>

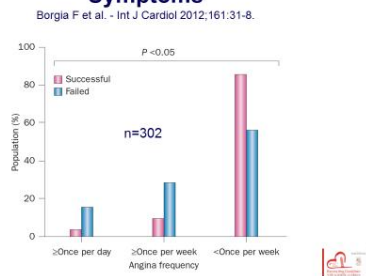
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Refractory angina: prevalence and pathogenetic mechanisms



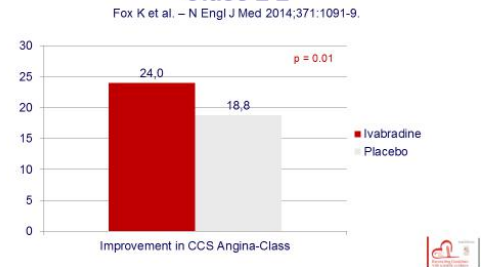
neither excellent medical nor excellent surgical therapy have managed to go beyond a success rate equal to 80% of the cases in ideal condition. There are also non-organic pathological conditions, such as depression, that give rise to an increase in the prevalence of angina. In the light of the guidelines, Prof. Sechtem therefore passed on to analysis

CTO-PCI Improves Anginal Symptoms



Prof. Sechtem from Stuttgart (D) addressed this decidedly current topic in view of the high percentage of patients who continue to be symptomatic despite the administration of an appropriate medical therapy. What can we do with patients suffering from refractory angina? The speaker used this question to introduce his talk, stressing the fact that

Antianginal Effect of Ivabradine in Patients With Angina CCS-Class ≥ 2



the data relating to the therapeutic options available for these patients, pointing out both their success potential and limits. In his conclusions, the speaker stated that in order to increase the therapeutic success rate it is fundamental to cure the states of anxiety and depression and to pay great attention to the patient's preferences when faced with the different therapeutic options.

- What are the ideal pharmaceutical products for patients suffering from refractory angina?
- What is the percentage of improvement in the therapeutic success due to the application of the PCI?
- What are the most effective therapeutic procedures in angina patients with depressive symptoms?
- Which pharmaceutical products could be added to the standard therapeutic protocol in refractory patients?
- What are the limits of medical treatment?
- What are the main therapeutic options?

To find the answer to these and other questions just click on this link:

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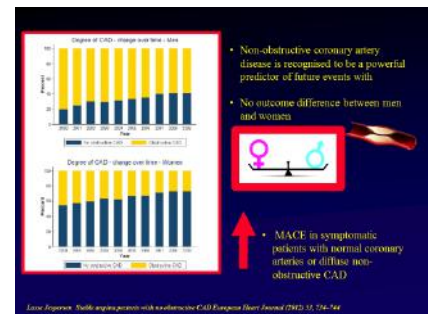
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Inappropriate use of non-invasive imaging techniques

Both the ACCF-AHA and ESC Clinical Practice Guidelines recommend revascularization on the basis of coronary anatomy as well as the extent of ischemia.

Organization	Reference	Key for Review to improve outcomes in patients with ischemia	Risk stratification by stress testing
ACCF/AHA	27	Class I—Angiography Class IIa—Angiography with ICD and/or catheter ablation Class IIb—Angiography with catheter ablation Class III—ICD and/or catheter ablation	Class I—Significant stenosis with inducible ischemia Class IIa—Significant stenosis with inducible ischemia Class IIb—Significant stenosis with inducible ischemia Class III—Significant stenosis with inducible ischemia
ESC guideline	18	Class I—Angiography with ICD and/or catheter ablation Class IIa—Angiography with ICD and/or catheter ablation Class IIb—Angiography with ICD and/or catheter ablation Class III—ICD and/or catheter ablation	Class I—Significant stenosis with inducible ischemia Class IIa—Significant stenosis with inducible ischemia Class IIb—Significant stenosis with inducible ischemia Class III—Significant stenosis with inducible ischemia
ACCF/AHA	28	Appropriate Class I—Angiography with ICD and/or catheter ablation Class IIa—Angiography with ICD and/or catheter ablation Class IIb—Angiography with ICD and/or catheter ablation Class III—ICD and/or catheter ablation	Class I—Significant stenosis with inducible ischemia Class IIa—Significant stenosis with inducible ischemia Class IIb—Significant stenosis with inducible ischemia Class III—Significant stenosis with inducible ischemia

Via the reading of the main trials conducted on the application of non-invasive imaging methods for diagnostic purposes, Dr. Morrone from Pisa demonstrated that the basing of the diagnosis of myocardial ischaemia on the presence and/or absence of atherosclerotic lesions at the coronary level is not a reliable procedure inasmuch as the presence of these lesions is not sufficiently indicative for being able to diagnose myocardial ischaemia. The speaker concluded her talk by stating that the use of anatomical tools for assessing the physiopathological processes is a clear example of inappropriate use of non-invasive imaging techniques.



Therefore...

Myocardial ischemia often occurs in patients without obstructive lesions and if most patients with obstructive CAD may be lifelong free from ischemia, how can we assess sensitivity and specificity of tests based on the presence or absence of Coronary atherosclerotic lesions?

Myocardial ischemia cannot be diagnosed from coronary anatomy

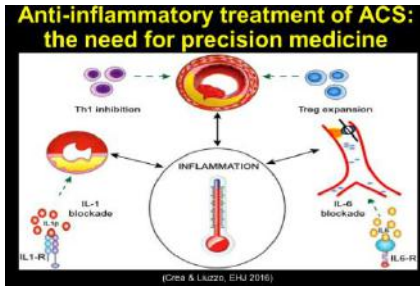
- What are the main recommendations published in the guidelines regarding the non-invasive diagnosis of ischaemic heart disease?
- What are the ideal tools for assessing patients suffering from stable angina?
- What are the most recent data published on the effects of the non-invasive tests?

To find the answer to these and other questions just click on this link:

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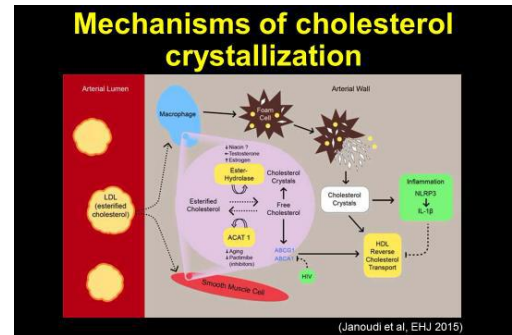
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Inflammation and myocardial ischaemia: which correlation links these two pathological phenomena?

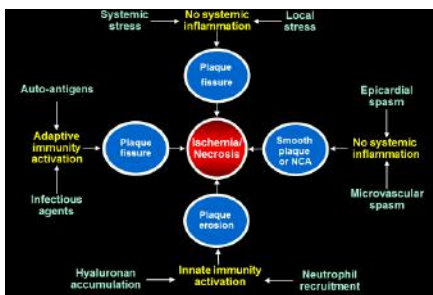


Prof. Crea from Roma (I) addressed this very current topic in the light of the studies and new discoveries over recent years. The speaker illustrated the main inflammation mechanisms that are able to determine conditions of myocardial ischaemia starting from the central point of the process; the presence of ischemia

and/or necrosis. During his talk, Prof. Crea built up an interesting physiopathological model that gives rise to the presence of the phenomena of ischemia and/or myocardial necrosis triggered by the presence of



infective agents, autoantigens, systemic or local stress, an accumulation of hyaluronic acid and neutrophils, and epicardial and microvascular spasm. The last part of his talk was dedicated to the “personalised” treatment of the acute coronary syndrome and the new and innovative therapeutic solutions that are now available.



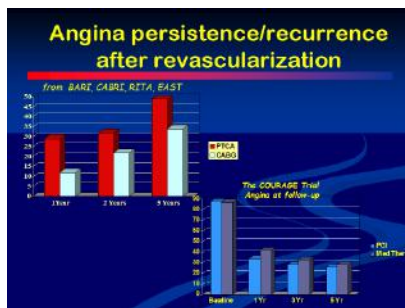
- What are the phenomena resulting from an increase or a reduction in the plasmatic levels of CD31?
- What are the key points of the anti-inflammatory treatment of acute coronary syndromes?
- What is the association between inflammation and cardiovascular events?
- What are the main mechanisms of crystallisation of cholesterol?
- What is the pathogenesis of the coronary spasm?
- What are the new therapeutic tools that allow for the personalised treatment of acute coronary syndromes?

To find the answer to these and other questions just click on this link:

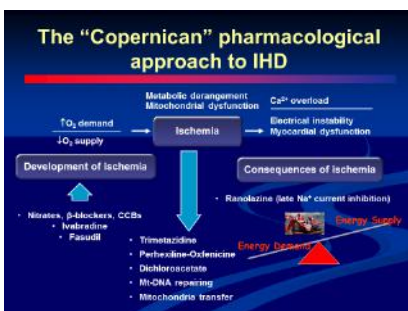
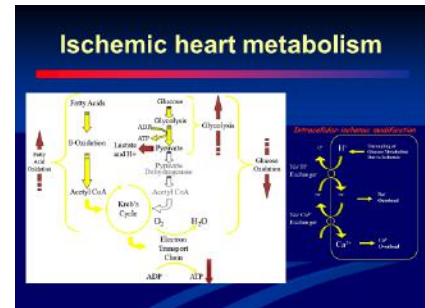
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and after logging in, access the multimedia material.

New therapeutic approaches for ischaemic heart disease



Starting from the consideration that the conventional treatment of ischaemic heart disease still shows significant margins of lack of success, Dr. Guarini from Pisa (I) presented recent data taken from clinical studies conducted on patients suffering from ischaemic heart disease who were treated with new therapeutic methods that act directly on the metabolism of the mitochondria of the myocardiocytes. The key point of this innovative approach is represented by the desire to intervene on the intimate metabolic defects affecting the mitochondria, by acting directly at a mitochondrial level. In the last part of her talk, she presented an integrated therapeutic model that combines the classical therapeutic methods with the innovative ones, defining it as a “Copernican” therapeutic approach for the treatment of the ischaemic heart disease.



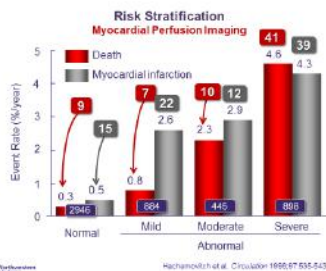
- What is the action mechanism of perhexilene?
- What is the effect of the trimetazidine on the oxidation processes of the free fatty acids?
- What is the action mechanism of ranolazine?
- What is the effect of ranolazine on recurrent ischaemic attacks in patients suffering from acute coronary syndrome?
- What is the action mechanism of Ivabradine?
- What is the action mechanism of Fasudil?
- What are the basics of the “Copernican” therapeutic approach for the treatment of the ischaemic heart disease?

To find the answer to these and other questions just click on this link:

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and after logging in, access the multimedia material.

Is the severity of stenosis a reliable predictor of ischaemic events?



Prof. Bonow from Chicago (USA) presented very interesting data on the prognostic value of the computerised angiography with regard to major cardiovascular events. The speaker emphasised how the pathogenic mechanisms responsible for acute coronary events are triggered by the interaction between microvascular disease and the instability of the non-stenotic coronary plaques. The data

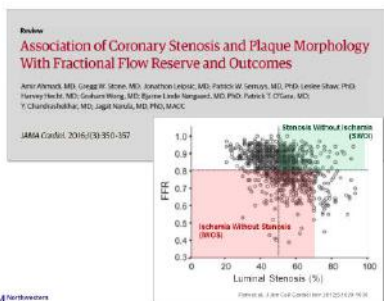
presented reveals how the angiographic technique, when applied for acquiring a prognostic evaluation in patients, is burdened by significant limitations since, as explained by Prof. Bonow, there is no direct, univocal correlation between the presence and evolution of the atherosclerotic

Acute Coronary Events in Patients Without Severe Coronary Stenoses

Mechanisms:

- Microvascular disease
- Instability of nonstenotic culprit plaques

plaque and major ischaemic events. The speaker concluded his talk by underscoring how acute coronary events can still be present in patients who have no signs of severe coronary stenosis. These phenomena are for the main part attributable to the presence of microvascular disease together with the presence of coronary plaques which are non-stenotic but which are characterised by a significant inflammatory state.



- What are the mechanisms that trigger acute coronary events in patients with no severe coronary stenosis?
- What are the main characteristics of the vulnerable plaque?
- What are the histopathological characteristics of the fibro-atheromatous plaque?
- What is the average progression time of a plaque before myocardial infarction?

To find the answer to these and other questions just click on this link:

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How can we predict the presence of resistant angina?

Stable Ischemic Heart Disease

Myocardial revascularization is performed with the aim of

- ✓ Reduce cardiovascular death
- ✓ Reduce MI
- ✓ Symptom relief

Study	Revascularization	MI	CV Death	Death
CASS	1/3	1.2	1.2	1.2
	2/3	1.2	1.2	1.2
CABOP	1/3	1.2	1.2	1.2
	2/3	1.2	1.2	1.2
CIB	1/3	1.2	1.2	1.2
	2/3	1.2	1.2	1.2
CIB-2	1/3	1.2	1.2	1.2
	2/3	1.2	1.2	1.2
CIB-3	1/3	1.2	1.2	1.2
	2/3	1.2	1.2	1.2



Stergiopoulos K et al. JAMA Intern Med. 2014;174(2):232-240

phenomenon are in fact not responsible at all, except in a very small part. The speaker took time to describe the so-called “other causes” of resistant angina, emphasizing the centrality of myocardial ischaemia in a physiopathogenetic

Dr. Huqi from Pisa (I) commenced her talk by dealing in a specific manner with the mechanisms responsible for resistant angina, starting from the consideration that between 15% and 50% of patients subjected to revascularisation still suffer from the symptoms of angina. One element emerging during her talk was that among these mechanisms, the ones classically indicated as explicative of this phenomenon are in fact not responsible at all, except in a very small part. The speaker took time to describe the so-called “other causes” of resistant angina, emphasizing the centrality of myocardial ischaemia in a physiopathogenetic model that considers the presence of factors such as inflammation, vasospasm, endothelial and microcirculatory dysfunction as the causal elements of myocardial ischaemia. In the last part of her talk, she gave a description of new early diagnosis protocols potentially capable of predicting the presence of resistant angina in patients suffering from angina.

Magnitude of the problem

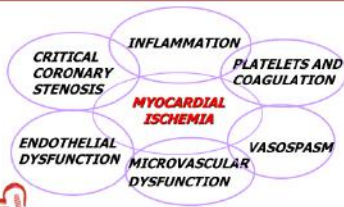
Following revascularization, a significant part of “optimally” treated patients, ranging **from 15 to more than 50%**,

present with

PERSISTENT ANGINA



Mentz BJ et al. Am J Cardiol. 2012;109(9):1272-1277.



Moravili et al. JACC Vol. 60, No. 11, 2012

- What are the main factors associated with the presence of resistant angina?
- What are the “alternative” mechanisms that explain the presence of resistant angina?
- Why is it necessary to apply therapeutic protocols deriving from the guidelines as the initial strategy?
- How important is the patient’s perception of the potential beneficial effects of the therapeutic protocol to be applied in terms of success?

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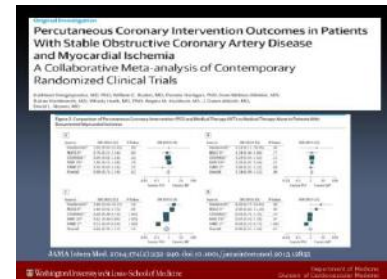
PCI versus optimal medical treatment: are there additional benefits?

Indications for Revascularization in Patients on OMT with SCAD

Indication	To improve prognosis		To improve symptoms		Ref.
	COR ^a	LOE ^b	COR ^a	LOE ^b	
A heart team approach to revascularization is recommended in patients with coronary artery disease (CAD) who have symptoms or complications.	C	B	C	B	(1), (2)
Left main CAD should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)
High-risk CAD (LAD disease) should be treated.	A	A	A	A	(1)

European Heart Journal, Oct 2010, 31 (24): 2999-3002

Prof. Brown from St. Louis (USA) addressed this topic by specifying that in order to be able to understand whether surgical techniques can produce additional benefits, it is necessary to make an assessment linked to the therapeutic intervention times and the current therapeutic context. Prof. Brown developed his talk by starting from the analysis of the guidelines and meta-analyses



conducted on this issue. The speaker pointed out how in all the trials conducted on patients suffering from ischaemic heart disease, in terms of outcome, those with the highest risk did not show any significant differences from one treatment to the next. Moreover, the revascularisation technique gives rise to complications that do not manifest

during the course of the medical therapy in addition to which it involves significantly higher costs. Prof. Brown concluded his talk by stating that in the absence of randomised, controlled clinical trials, designed in such a way as to eliminate the biases that are present in post-hoc trials and other similar types of studies, medical therapy should be considered the standard treatment in these types of patients even if the guidelines state the opposite.

PCI for SIHD: The Cost of Equipoise

	Current 400,000	50% Reduction	70% Reduction
Deaths (0.2%)	800	400	240
MI (2%)	8000	4000	2400
Cost (Billions)	\$10	\$5	\$3

Department of Medicine, Division of Cardiovascular Medicine

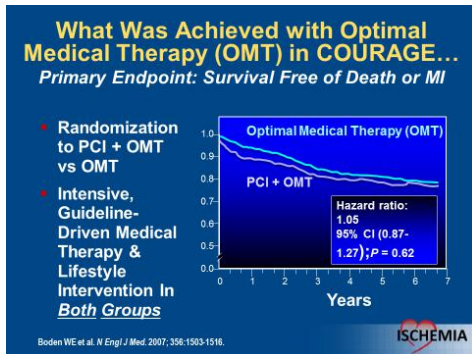
- What are the indications contained in the guidelines on the treatment of coronary revascularisation?
- What are the results of the comparative clinical trials between PCI and optimal medical treatment in terms of outcome for patients suffering from ischaemic heart disease?
- What are the main complications linked to the treatment with PCI?
- What are the costs of the treatment with PCI?

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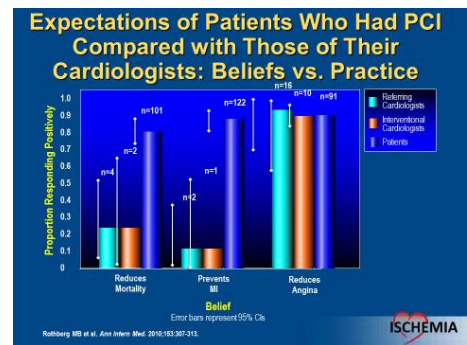
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Why do we revascularise the patient: for anatomical reasons, because of ischaemia or for psychological reasons? And what does all this have to do with scientific evidence?

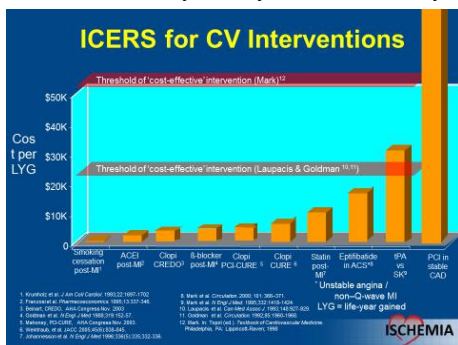


Prof. Boden from Albany (USA) addressed this topic starting from the viewpoint that the treatment of the ischaemic coronaropathy was imposed on the basis of the assessments of an anatomical type, especially starting from the implementation of the PCI, used principally for patients suffering from myocardial infarction. This was subsequently also applied to patients with stable coronary disease in whom medical therapy presents a similar

percentage of therapeutic successes as those obtained with the revascularisation technique. The speaker continued with this topic by examining the main randomised, comparative clinical trials between PCI and excellent medical therapy in patients with coronary disease of varying degrees of severity. This analysis was completed with two other evaluations, one of pharmacoeconomics and the other based on the perception of the patients. In his conclusions, the speaker stressed how patients



suffering from ischaemic coronaropathy continue to be re-vascularised and the medical therapy continues to be underused despite the fact that the data published in the randomised, controlled clinical trials clearly indicate that revascularisation techniques fail to give rise to any benefits in terms of outcome compared to excellent medical therapy, and how much the latter entails a significantly lower number of adverse events and/or complications.



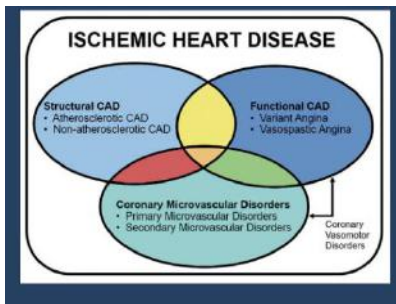
- What is the percentage of the reduction of events attributable to the implementation of the revascularisation techniques?
- What is the percentage of the reduction of events attributable changes in lifestyle?
- What is the level of costs reached with the extensive application of the revascularisation techniques?
- What are the expectations of patients who choose to undergo a revascularisation operation?

To find the answer to these and other questions just click on this link:

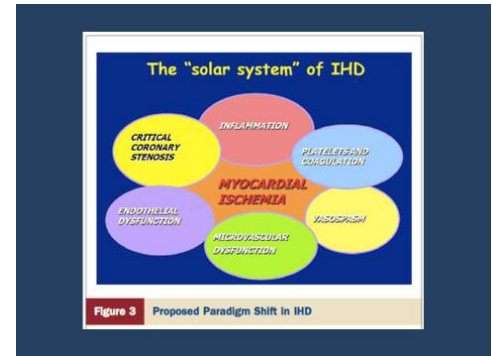
<http://www.fondazione-menarini.it/Archivio-Eventi/2016/4th-International-Summit-on-Ischemic-Heart-Disease-Reconciling-Guidelines-with-scientific-evidence/Materiale-Multimediale>

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The Copernican revolution in ischaemic heart disease: progress and errors



Prof. De Maria from La Jolla (USA) addressed the topic of ischaemic heart disease by comparing the latest acquisitions over the recent years with the Copernican revolution that starting from the sixteenth century radically changed in just on 200 years not only the knowledge of physics and astronomy but also the very perception of the world at that time.



Following this comparison, the speaker focussed his attention on the microvascular dysfunction by analysing the diagnostic procedures and the therapeutic options currently available. On various occasions during his talk, Prof. De Maria emphasised the need to implement both

cognitive and time resources for the purpose of changing the cultural attitude of the medical class convinced as it is that it knows everything about ischaemic heart disease. In his conclusions, the speaker pointed out how this cultural revolution must pass through the five stages represented by the massive publication of articles that have an impact on the guidelines, from the training of a new scientific society to the publishing of a new scientific journal and the presentation of new work at scientific meetings specifically designed to deal

- Progress from 2014**
- Publish articles
 - Appear in Guidelines
 - Form a Society
 - Publish a Journal
 - Present at Meetings

with this issue.

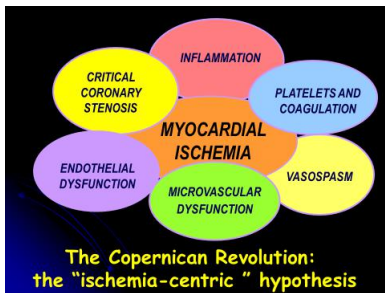
- What are the main incongruencies between occlusive coronaropathy and ischaemic heart disease?
- What are the main characteristics of the microvascular dysfunction?
- Which therapeutic strategies are currently available for treating ischaemic heart disease?
- What are the key points of the new centric ischaemic theory?

To find the answer to these and other questions just click on this link:

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Ischaemic heart disease in 2016: prospects and training requirements



At the end of the congress works, Prof. Marzilli from Pisa (I), chairman of the convention, forcefully reiterated the value of the centric ischaemic theory, stressing the need to diagnose and treat ischaemic heart failure rather than coronary stenosis. During his talk, Prof. Marzilli took into account the main problems that create

obstructions to this cultural revolution, linked to the methods used to design randomised clinical trials, and to the impact that evidence-based medicine has on the guidelines and on industry-based medicine. The

speaker concluded his talk by emphasising the need to launch cultural messages capable of having an impact on medical practice in the aim of enhancing its ongoing improvement.

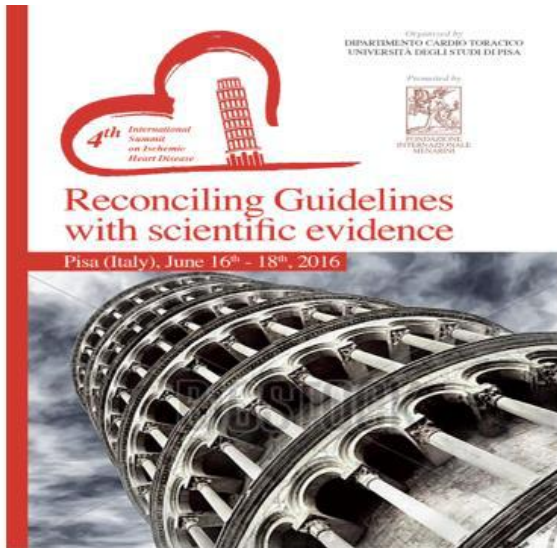


- What are the operational proposals advanced by the speaker for providing incentives for correct medical training in this field?
- What are the main limits of clinical trials pointed out by the speaker?
- What could the impact be of a new small scientific society on the most important scientific societies that have been present in cardiology for years?
- What is the trend of revascularisation interventions in the United States?

To find the answer to these and other questions just click on this link:

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These are just some of the topics addressed during the congress works.

For a more in-depth analysis please visit the website of the Fondazione Internazionale Menarini which also contains the full version of the congress talks.

To follow the presentations of this convention just click on this link: <http://www.fondazione-menarini.it/Archivio-Eventi/2016/4th-International-Summit-on-Ischemic-Heart-Disease-Reconciling-Guidelines-with-scientific-evidence/Materiale-Multimediale> and after logging in, access the multimedia material.